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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,586	11/30/2000	Michael Kock	49100	5846

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/701,586	KOCK ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 33-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 33-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment of claims 1-3 and the addition of new claims 33-60, in the paper of 3/10/2008, is acknowledged.

Claims 1-3 and 33-60 are at issue and are present for examination.

Applicants' arguments filed on 3/10/2008, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claims 34-37, 39-46, 48-60 are objected to because of the following informalities: Claims 34-37, 39-46, 48-60 each depend from a different claim and recite the claim they depend from, followed by "further comprising…" It is suggested that in each of these claims a comma be inserted before the word "further".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Newly added claims 34-37, 39-43 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34-37, 39-43 and 52 are indefinite in that it is unclear and confusing as to applicant's intent in the recitation "part-sequence motif". The confusion results from

applicant's reference to some sequence motifs as "sequence motifs" and others as "part-sequence motifs". Given the different terminology of what appears to be a sequence motif, it is unclear as to the claimed subject matter of the referenced claims. Applicant's specification at page 5, lines 15 through 27, similarly refers to "part-sequence motifs" and does not offer clarification.

Claim 44 is rejected under this statue on the basis that claim 44 recites "$GX_3LXVALG$ (SEQ ID NO: 20)". The sequence listed as SEQ ID NO: 20 is wrong, as it is missing an "E" and should be "$GX_3LXEVALG$". For the purpose of advancing prosecution, this is how this recitation is interpreted.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 33-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a poly(ADP-ribose) polymerase (PARP) homolog comprising the amino acid sequence of SEQ ID NO: 2, does not reasonably provide enablement for any poly(ADP-ribose) polymerase (PARP) homolog and functional equivalents thereof which is at least 85% homologous thereto, and has a functional NAD^+ binding domain with the sequence $PX_n(S/T)GX_3GKGIYFA$, wherein n is an integral value from 1 to 5, and lacks a zinc finger motif with the sequence $CX_2CX_MHX_2C$, wherein M is 28 or 30. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the invention commensurate in scope with these claims. New claims 33-60 are included in this rejection for the same reasons as previously stated for claims 1-3.

This rejection was stated in the previous office action as it applied to previous claims 1-3. In response to the rejection applicants have amended claims 1-3 and added new claims 33-60 and argued the rejection as it applies to the newly amended/added claims.

Applicants submit that they have provided specific guidance for the modification of PARPs, including the ability "to replace certain amino acids with those of similar physiochemical properties (bulk, basicity, hydrophobicity, etc.)" and provide examples of such substitutions, e.g. arginine for lysine.

Applicants submit that the previous assertion by the examiner that modification of the specific amino acid positions within a given protein sequence is unpredictable and that one of skill in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, is untenable. Applicants submit that "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement" (439F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)(emphasis in original)).

Applicants submit that the Examiner's assertions regarding substituting amino acids, the predictability of results and obtaining the desired activity in the end product

are not accurate, as applicants submit that one of ordinary skill in the art would be able to determine to a sufficient degree, as to not require undue experimentation, amino acid substitutions. First, a skilled artisan would know that in certain positions, certain amino acid changes would render the subsequent protein inactive and would avoid using said substitutions and second, computational techniques were available at the time of filing for protein structural predictions based on sequence listings.

Applicants submit that in this regard, The Examiner has provided no evidence to support the assertions of undue experimentation. Applicants submit that in order to establish a *prima facie* rejection, the Examiner must provide evidence of the necessity of said "undue experimentation." Along these lines, the Examiner has not stated why one skilled in the art could not supply the allegedly needed enabling information without undue experimentation.

Applicant's complete argument is acknowledged and has been carefully considered, however, is not found persuasive on for the reasons previously made of record and repeated herein.

With respect to applicants submission that they have provided specific guidance for the modification of PARPs, including the amino acid sequence of SEQ ID NO: 2 and the ability "to replace certain amino acids with those of similar physiochemical properties (bulk, basicity, hydrophobicity, etc.)" and provide examples of such substitutions, e.g. arginine for lysine, while such is helpful in adding to necessary guidance so as to enable the full breadth of the claim, this is by itself insufficient given the skill in the art and the size of the PARP protein to be mutagenized.

Applicants argument is not found percussive on the basis that the breadth of applicants claimed genus continues to be broad enough that while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as encompassed by applicants claims and eluded to in applicants arguments requires that one of ordinary skill in the art know or be provided with sufficient guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting poly(ADP-ribose) polymerase activity; (B) the general tolerance of poly(ADP-ribose) polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a poly(ADP-ribose) polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

As was previously stated, because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be

acceptable to retain the poly(ADP-ribose) polymerase activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable as evidenced by Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, it would require undue experimentation for one skilled in the art to arrive at the majority of those polypeptides of the claimed genus.

With respect to applicants assertion that the skilled artisan would know that in certain positions, certain amino acid changes would render the subsequent protein inactive and would avoid using said substitutions and that computational techniques were available at the time of filing, for protein structural predictions based on sequence listings are acknowledged and while generally relevant do not address the problems associated with the particularities of the specifically claimed protein.

Applicants submit that in this regard, the Examiner has provided no evidence to support the assertions of undue experimentation. Applicants submit that in order to establish a *prima facie* rejection, the Examiner must provide evidence of the necessity of said "undue experimentation" and the Examiner has not stated why one skilled in the art could not supply the allegedly needed enabling information without undue experimentation.

The basis of the rejection remains as was previously stated. Applicants reference human poly(ADP-ribose)polymerase is a 570 amino acid sequence protein that is insufficient to enable the breadth of the claimed genus of which applicants are

claiming to any functional equivalent thereof which is at least 85% homologous thereto and exhibits poly(ADP-ribose)-synthesizing activity and also has a functional NAD+ binding domain comprising the sequence motif $PX_n(S/T)GX_3GKGIYFA$ (SEQ ID NO: 11). Those claimed subgenuses which require additional motif sequences are somewhat more sufficiently enabled, however, remain rejected on the basis that scope of the claimed functional equivalents comprising additional motifs remains overly broad to enable the claimed genus of functional equivalents.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the claimed poly(ADP-ribose) polymerase functional equivalents. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Of note, applicants reference to “at least 85% homologous thereto” is not necessarily limited to amino acid sequence homology and may be interpreted as "functional homology", an issue which does not help applicants meet the requirements of 112 first paragraph.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rgh
5/19/2008

/Richard G Hutson, Ph.D./
Primary Examiner, Art Unit 1652